REMARKS

Claims 50-60, 64-71, 73, 75-77, 79, 81 and 83-93 stand pending in the present application. By this Amendment, Applicants have amended claims 50, 56, 57, 64 and 65 and canceled claims 61 and 62. Applicants respectfully submit that the present application is in condition for allowance for the reasons as set forth below.

The Examiner noted that the drawings filed on September 9, 1999 are not in compliance with 37 C.F.R. § 1.84(a). Applicants are in the process of preparing formal drawings and will submit them in due course but no later than at the time of payment of the Issue Fee.

The Examiner objected to the Abstract filed on June 18, 2001 as not being on a separate sheet as required by 37 C.F.R. § 1.72(b). Applicants respectfully submit that this requirement in a national stage 371 application is "improper" (see MPEP, § 1893.03(e)) since the PCT published application contained an Abstract on a separate page. Therefore, Applicants respectfully request that the Examiner withdraw the objection to the specification as filed on June 18, 2001.

The Examiner rejected claims 50-62, 64-71, 73, 75-77, 79, 81 and 83-93 under 35 U.S.C. § 112, first paragraph administering to a prospective mother, a sperm antigen of a prospective father and substantially purified TGFβ, on the grounds that the specification, while being enabling for a method of eliciting an immune reaction in a prospective mammalian mother to sperm antigens of a prospective father to alleviate symptoms of an infertility condition, said method comprising the method leading to tolerance of the sperm antigen and alleviation of the infertility condition, did not provide enablement for a method of eliciting *any* immune reaction in a prospective mammalian

mother using (1) *any* one or more antigens, (2) *any* antigen on either the sperm or the conceptus, (3) *any* MHC antigens, (4) *any* modified TGFβ, (5) *any* TGFβ wherein the modification comprises substitution, deletion, or addition mutants, (6) *any* peptide fragments of TGFβ, and (7) *any* derivative or analog thereof leading to tolerance to any antigens and alleviation of the infertility condition.

Further, the Examiner has noted in Section 9 of the outstanding Office Action that the specification discloses a method of eliciting an immune response of a prospective mother to sperm antigens by co-administering the antigens and the TGFβ in order to induce tolerance and for alleviating the symptoms of infertility.

Without prejudice, and in an effort to progress the ultimate allowance of the present application by this Amendment, and without addressing the merits of the Examiner's 35 U.S.C. § 112, first paragraph rejection of the claims, Applicants have amended the claims to recite the method the Examiner conceded was clearly enabled, namely a method for eliciting an immune reaction to a prospective mammalian mother to one or more MHC Class I antigens of a prospective father and substantially purified TGFβ, thereby to induce tolerance to the antigens. Essentially, claim 50 has been amended to include the subject matter of now canceled claims 61 and 62.

The amended claims specify that the TGFβ which may be selected from the group consisting of $TGF\beta_1$, $TGF\beta_2$ and $TGF\beta_3$ and activin. Applicants submit that all types of TGFβ are enabled by the disclosure in the specification as filed.

Furthermore, with reference to the Examiner's comments on the use of fragments and analogues of TGF-β, which are specified only in claims 73 and 75, it would be perfectly clear to one of ordinary skill in the art from the specification, that *any*

TGFβ molecule which induces GM-CSF production could be used for the purposes of the invention. For example, the specification at pages 18 and 19 describes an assay system which may readily be used to determine whether a given TGFβ molecule is suitable. A wide variety of fragments and analogues of various TGFβ molecules is known, and their sequences have been published; see, e.g., the Tuan et al or Lyons et al references referred to by the Examiner in item 16. See also the attached Rule 132 Declaration of Professor David Clark ("Clark Declaration"), paragraph 10.

Insofar as the breadth of the term "TGFβ" is concerned, the Examiner appears to have overlooked the fact that Figure 4 of the specification as filed clearly shows that *both* $TGF\beta_1$ and $TGF\beta_2$ in seminal plasma elicit GM-CSF stimulating activity. There is also ample evidence in the art of commonality of function between the three subclasses of TGFβ, including:

(a) The mature peptide sequences of the three mammalian TGFβs isolated to date have 70-80% similarity to the amino acid level largely due to the conserved cysteine knot structure. The TGFβ subfamily isoforms activate through similar signaling cascades, which are initiated by binding of TGFβ to heteromeric complexes of type I and type II TGFβ receptors at the surface of target cells; (reviewed by Lawrence, 1996; a copy of which is enclosed with this Amendment.)

(b) The three mammalian TGFβs possess similar activities: they inhibit proliferation of most cells, but can stimulate growth of some mesenchymal cells; they enhance the formation of extracellular matrix and they exert immunosuppressive effects (reviewed by Lawrence, 1996);

(c) All three mammalian TGFβs are recognized to have effects on immune cells, including all classes of lymphocytes, macrophages and dendritic cells (reviewed by Letterio and Roberts et al., 1998; copy attached). The mammalian TGFβs all have pleiotrophic and profound effects on the immune system and on hematologic malignances. In fact the mammalian TGFβs have been described as the most potent immunosuppressor described at the time of publication and evidence exists that the immunosuppressive potential of TGFβ is an important promoter of malignant cell growth due to its immunosuppressive properties (reviewed by Ruscetti et al., 1993; a copy of which is enclosed with this Amendment).

Moreover, Applicants have now obtained further experimental results, which clearly show that all three isoforms of TGFβ are able to induce release of GM-CSF from human cervical keratinocytes. In particular, Applicants attach herewith a Rule 132 Declaration by Professor David Clark, an independent expert in the field of reproductive immunology ("Clark Declaration"),[1]. The Clark Declaration attests to the effective interchangeability of $TGF\beta_1$, $TGF\beta_2$ and $TGF\beta_3$. Professor Clark is the senior author of the reference by Clark et al, Human Reproduction (1994), 9, 2270-7, which has been cited by the Examiner.

The Examiner has stated that the prior art teaches that the functions of $TGF\beta_1$, $TGF\beta_2$ and $TGF\beta_3$ and analogues thereof, including activin, are distinct and largely non-overlapping, based on targeted disruption of the three $TGF\beta_1$ genes. Although Applicants acknowledge that there are some differences in biological activity between

[1] An executed copy of this Declaration with cited Exhibits will follow shortly.

the isoforms, it is in fact the case that there are also many shared characteristics between the isoforms.

The Examiner has stated that it is unpredictable, given the state of the art, that TGFβ isoforms other than $TGF\beta_1$ would work. However, this merely further evidences that the Examiner has basically overlooked many of the essential teachings of the present specification, in particular the information as set out in Figure 4 of the application as filed. Figure 4 shows that $TGF\beta_1$, $TGF\beta_2$ and activin are all able to elicit a GM-CSF response, which is stated in the specification to be necessary to start the immune cascade which will alleviate the infertility condition.

This observation that $TGF\beta_1$, $TGF\beta_2$ and activin are able to elicit GM-CSF production represents a common mode of action of all three isoforms, although it is not known at this stage whether or not other critical reactions are involved. The original specification thus clearly demonstrates that $TGF\beta_1$, $TGF\beta_2$ and activin are able to trigger the Type 2 response. The activation of this cascade leads to the stimulation of antigen-presenting dendritic and macrophage cells, their consequent invasion of the stromal tissue, and increasing intensity of antigen signaling to the lymph nodes, which are necessary for alleviating an infertility condition. The Examiner has no basis for stating that it cannot be predicted from the specification whether other TGFβ isoforms would work.

Accordingly, there is no question that given the disclosure of the specification, a person of ordinary skill in the art would be able to carry out the invention using all three isoforms of TGFβ, without the need for a further inventive step or for an undue degree of experimentation. In fact, once provided with the disclosure in the specification it would

be a matter of mere routine for such a person of ordinary skill in the art to carry out the necessary experiments. This is demonstrated by the Rule 132 Declaration by David Sharkey ("Sharkey Declaration"), a copy of which is submitted along with this Amendment. Contrary to the Examiner's assertions, the experiments conducted as reflected in the Sharkey Declaration showed that any of the three TGFβ isoforms, namely $TGF\beta_1$, $TGF\beta_2$ and $TGF\beta_3$, was able to elicit the GM-CSF response in tissues derived from the human female reproductive tract. Please note, this experiment was *ex vivo* not *in vivo* by David Sharkey, a graduate student pursuing Ph.D. studies, and thus he not considered a skilled expert in the field, but rather a person of lower ordinary skill. Therefore, certainly, one of ordinary skill in the art would readily appreciate the applicability of any of the TGFβ isoforms.

The specification also demonstrates that antibodies which are directed to all three isoforms, $TGF\beta_1$, $TGF\beta_2$ and $TGF\beta_3$, could block the entire GM-CSF stimulating activity in seminal plasma, whereas an antibody specific for $TGF\beta_1$, administered alone, could only block 86% of the GM-CSF activity (see Figure 2 of the specification and Sharkey Declaration, paragraph 11).

Accordingly, the Examiner is incorrect in overlooking the teachings such as provided in Figure 4 and instead pointing to a single publication which alludes to the possibility of some functional differences between the isoforms. While the Applicants acknowledge that there may be some slight functional differences between the TGFβ isoforms, it is in fact the case that there are many shared functional characteristics, and that as outlined above, any of the TGFβ isoforms was able to elicit the GM-CSF response in tissues derived from the human female reproductive tract.

In view of the foregoing, Applicants respectfully submit that the claims as amended are enabled. Therefore, Applicants respectfully request that the 35 U.S.C. § 112, first paragraph rejection to the claims be withdrawn.

Claims 56 and 65-67 were rejected under 35 U.S.C. § 112, second paragraph. By this Amendment, Applicants have amended claims 56, 64 and 65, thereby obviating the 35 U.S.C. § 112, second paragraph rejection.

Claims 50-62, 64-67, 70, 73, 79, 77, 81, 85, 86, 89, 90, 92 and 93 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,395,825 ("Feinberg") in view of Clark et al (Hum Repro 9(12):2270-7, Dec. 1994, PTO 892; hereinafter "Clark 1994"), Chaouat et al (J. Immunology 134(3):1594-8, March 1985; PTO 892; hereinafter "Chaouat"). This rejection, insofar as applied to the claims as amended, is respectfully traversed for the following reasons.

Feinberg teaches the use of TGFβ for stimulating the production of trophoblast fibronectin for increasing the success rate of implantation. However, the only experimental evidence in Feinberg is exclusively directed to the study of trophoblast cells which appear only after implantation. Although Feinberg does disclose treatment of either a conceptus, i.e., an embryo, an ovum, or sperm, with TGFβ either prior to, simultaneously with, or following introduction into the reproductive tract of a female mammal, with a view to increasing the success rate of implantation, there is absolutely no mention of immune tolerance. The only examples in Feinberg relate to the identification of a so-called tropho-uteronectin released by trophoblast cells in culture, in response to a stimulating factor present in serum. Release of tropho-uteronectin was

also stimulated by TGFβ_1, and blocked by a TGFβ antibody (examples 1-4). TGFβ also increased attachment of trophoblasts to a surface.

Feinberg fails to provide an enabling disclosure with regard to the role of a TGFβ *in vivo*. There is absolutely no evidence in Feinberg to suggest that in fact treatment of an ovum or a sperm with TGFβ would improve implantation of an embryo. Moreover, there is no suggestion that a prospective mother should be exposed to sperm of a prospective father together with TGFβ prior to attempted conception, or after attempted conception, or that the TGFβ and the antigen of the prospective father should be administered at different times. In other words, the only scenario presented by Feinberg for exposure to a paternal antigen is via artificial insemination or embryo implantation *together with* TGFβ. See Clark Declaration, paragraphs 24 and 25.

Feinberg refers only to the "competence of a conceptus towards uterine implantation (column 3 line 50) and methods of increasing the success rate of *assisted* reproduction (column 3 lines 66 to 67), and is completely silent regarding antigens of any kind, immunization of the prospective mother, or immune tolerance. The only mention of any immune factor is at column 4 lines 38 to 47, which states that the invention provides methods of contraception and contragestion comprising administering a TGFβ *antagonist*, such as antibodies to TGFβ, in order to increase the probability that conception will be *prevented*. This is completely opposite to the presently-claimed invention, wherein a TGFβ must be administered to increase the probability that a fertilized ovum will succeed in generating a liveborn offspring. See Clark Declaration, paragraph 24.

Feinberg fails to provide any actual experimental evidence to suggest that:

a) treatment of an ovum or sperm would improve implantation,

b) the prospective mother would be exposed to sperm of a prospective father together with TGFβ either prior to or after attempted conception, or

c) the TGFβ and antigen of the prospective father should be administered to the prospective mother at different times. See Clark Declaration, paragraph 25.

Feinberg suggests that stimulation of fibronectin production by a fertilized ovum by a TGFβ should enhance outgrowth of trophoblast which is essential in the process of implantation, which in reality occurs only *in vivo*. However, Feinberg provides experimental evidence only for treatment of the mother *after* implantation. Since Feinberg provides no demonstration that implantation is enhanced, the proposed biological role of a TGFβ *in vivo* represents untested speculation. Therefore, Feinberg fails to provide an enabling disclosure with regard to the role of a TGFβ *in vivo*. See Clark Declaration, paragraph 25.

In sharp contrast to Feinberg, the claimed invention involves treating *the mother* to induce immune tolerance *prior to conception*. In other words, Feinberg discloses an entirely different method, in which the timing of administration of the paternal antigen is different, as well as the procedure as a whole having a different aim.

The Examiner has acknowledged that in fact the present invention as defined in the claims is distinguished from Feinberg. Consequently, this reference is relevant only when combined with one or more of the other two references relied upon by the Examiner in item 14. However, there is no teaching or suggestion in any of the three cited references which would provide motivation for a person of ordinary skill in the art to make such a combination. Moreover, there are significant differences between the

claimed invention and the references by Clark et al. and by Chaouat et al. which would lead a person of ordinary skill in the art away from making such combinations.

The Examiner considers that Clark 1994 discloses that TGFβ has immunosuppressive activity *in vivo* during the first trimester pregnancy in humans. Clark 1994 can be distinguished from the claimed invention on the basis of the following points which are further elaborated in the Clark Declaration and in particular, paragraph 26:

Clark 1994 discloses the up-regulation of *endogenous* TGFβ release by $CD56^+$ cells in decidua during the first trimester, i.e., after conception and implantation. The decidua is the inner layer of the wall of the uterus, which envelopes the embryo and forms part of the placenta. Thus it is a tissue of *maternal* origin.

The claimed invention recites the administration of substantially purified, i.e., *exogenous* TGFβ to the mother *prior* to conception or to embryo transplantation. Clark 1994 clearly teaches away from this, as Clark 1994 does not disclose or suggest the administration of purified TGFβ at all, let alone administration of TGFβ in conjunction with one or more antigens of a prospective father.

In the human body, TGFβ is produced by many cells for many different purposes, including immunosuppression, growth regulation, cell transformation, cell migration, embryo development, implantation, support for sperm and immune activation. While Clark 1994 teaches the up-regulation of TGFβ post-implantation, this reference does not definitely show any role of TGFβ during pregnancy, and certainly does not demonstrate any role of TGFβ prior to conception, as the inventors have done. It is merely proposed in the introduction and discussion sections of this paper that $TGF\beta_2$ and related

molecules inhibit maternal cytotoxic cells, which are potentially able to reject the embryo during the first trimester of pregnancy. Even if Clark 1994 had confirmed this proposed function of $TGF\beta_2$, this does not suggest the role of TGFβ in seminal plasma and the role of *exogenous* TGFβ administered prior to conception.

In fact, there are a large number of cytokines present during conception and pregnancy which may act as immunosuppressors, including IL-6, prostaglandin E, hydroxyprostaglandin E, and HLA-G; therefore, Clark 1994 fails to disclose which factor is the *principal* factor which is required before conception in order to elicit the immune tolerance against the conceptus, as taught in the applicant's specification.

Furthermore, Clark 1994 does not disclose or suggest that the type and magnitude of the immune suppression caused by the TGFβ prior to conception would be sufficient for induction of immune tolerance against the conceptus and to alleviate the infertility condition.

Chaouat discloses that foetal viability in mice in which the pregnancy results from mating between one particular histo-incompatible male-female combination is increased if the female is immunized with spleen cells of another histo-incompatible mouse type, *not* by immunization with the paternal cells. This immunization induces MHC antibodies against the paternal antigens which are predominantly of the IgG1 class, and which rapidly disappear from the maternal serum during pregnancy. There is increased active immunosuppression in both spleen and placenta. However, Chaouat provides absolutely no disclosure or suggestion that TGFβ might play any role. Indeed, the statement at page 1598, column 1, that "one obvious candidate is the IgG1 anti-paternal MHC antibody" teaches away from any such proposal. All that is established is that a

serum component with specificity for the H-2 histocompatibility complex is capable of reducing the high rate of spontaneous resorption of the foetuses in this particular strain combination, and that this correlates with an increase in placental active suppression.

The finding by Chaouat that immunization of a female mouse with spleen cells of a histoincompatible mouse increases fetal viability fails to suggest that immunization with antigens such as MHC CLASS 1 antigens, would be useful for treatment of infertility. On the contrary, as discussed in the Clark Declaration, Chaouat in fact shows that prevention of spontaneous abortion in DBA/2-mated CBA/J mice could *not* be prevented by immunizing the CBA/J female against the Class I MHC of the DBA/2 male. It was necessary to use spleen cells from BALB/c mice. The BALB/c mouse strain is regarded as having the *same* H-2^d Class I MHC antigen as the DBA/2 strain, and from Kiger et al (J Immunol 1985), it was subsequently known that minor non-MHC antigens on the BALB/c mouse background were required along with the H-2^d MHC antigens. Antibodies are rarely if ever made against minor non-MHC antigens. Data from studies in which women were immunized against their husband's HLA-incompatible blood mononuclear cells (e.g., Mowbray 1986) indicated that an antibody response to MHC was not required for prevention of miscarriages. It was known from Clark 1994 that immunization of mice which prevented abortions increased the level of production of the novel TGFβ2-related factor mentioned above, but this should not be taken to indicate that the effect arose from an immune response to the paternal Class I MHC antigens. In fact no published study has shown that immunity to paternal Class I MHC antigens alone can improve the rate of implantation. See the attached Clark Declaration, paragraph 27.

Given this failure of the references by Clark 1994 and by Chaouat to disclose or even suggest immunization with a paternal antigen (Clark 1994), or administration of TGFβ (Chaouat) respectively, there is absolutely no motivation whatsoever to combine either or both of these references with the disclosure by Feinberg. It would therefore not have been obvious at the claimed priority date for a person of ordinary skill in the art to do so.

Moreover, there would additionally be no motivation to administer TGFβ and one or more antigens at all, or systemically, at a first and a difference site, with TGFβ in an unpurified form, or using multiple exposure to TGFβ and antigen. In view of the foregoing, it is submitted that claims 50-60, 64-67, 70, 73, 77, 79, 81, 85, 86, 89, 90, 92 and 93 are novel and not obvious in view of the cited references, and that the Examiner's rejections on the basis of these references is respectfully traversed.

Claims 66-67 and 71 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,395,825 in view of Clark 1994, Chaouat, and further in view of Harlow et al (hereinafter "Harlow") and Martin-Villa et al (hereinafter "Martin-Villa"). This rejection, insofar as applied to the claims as amended, is respectfully traversed for the reasons that follow.

With regard to the rejection of claims 66-67 and 71, the additional references cited by the Examiner in these items represent features which would only have been obvious to combine with the administration of a TGFβ in conjunction with an antigen of a prospective father *once in possession of the present invention as defined in claim 50 (twice amended)*. Moreover, two of the references relied upon by the Examiner in paragraph 16 relate to modifications of TGFβ, including fragments and analogues. The

Examiner's reliance on these references is completely inconsistent with the enablement rejection under section 112 in relation to fragments and analogues and other modifications of TGFβ. It would not have been obvious to utilize the references by Grainger et al. or by Heidenreich et al for the purposes stated by the Examiner without knowing of the present invention as defined in claim 50.

Moreover, the reference by Heidenreich is completely irrelevant to the present invention, as is perfectly evident from the abstract. This shows that Heidenreich was examining the presence of anti-sperm antibodies *in infertile men*, as a possible explanation for their infertility. This would in no way lead a person of ordinary skill in the art to attempt to induce immunological tolerance *in a prospective mother* in order to alleviate an infertility condition affecting either the mother or the couple. Accordingly, the Examiner's rejection of Claims 66-67 and 71 is respectfully traversed and should be withdrawn, and Applicants respectfully submit that all pending claims are not anticipated by nor made obvious in view of the cited references for the reasons as stated above.

In light of the present amendments and arguments as set forth above, Applicants respectfully submit that all prior rejections have been overcome, and that this application is now in condition for allowance. Such action is earnestly solicited.

Respectfully submitted,

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ATTACHMENT A

Marked Up Replacement Paragraphs

At the following locations, a marked up copy of the replaced paragraph is provided.

Page 1, lines 17-19:

In the context of this ~~patent~~ specification an infertility condition is to be understood to relate not only the capacity to conceive but also to miscarriage, spontaneous abortion or other pregnancy-related conditions, such as pre-eclampsia, and includes sub-fertility.

Page 4, lines 14-29:

The temporal changes in trafficking and phenotypic ~~behaviour~~ behavior of endometrial leukocytes during the period between mating and implantation are likely to be orchestrated principally by cytokines emanating from steroid hormone regulated epithelial cells lining the endometrial surface and comprising the endometrial glands (8). Of particular importance are granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-(IL)-6, the synthesis of which ~~are~~ is upregulated at least 20-fold and 200-fold respectively in estrogen primed epithelial cells following induction by specific proteinaceous factors in seminal plasma (8.9) known to be derived from the seminal vesicle gland (10). Previous studies have implicated the surge in epithelial GM-CSF release as a key mediator in the post-mating inflammatory response since injection of recombinant GM-CSF into the estrous uterus is sufficient to produce cellular changes resembling those seen following natural mating (11). The inventors have found, using GM-CSF deficient mice, that the chemotactic activity of GM-CSF is likely to

be compensated or augmented by an array of chemokines, the expression of which ~~are~~ is transiently upregulated after mating (12), and cytokines synthesised by activated endometrial macrophages including IL-1 and tumour necrosis factor-α (TNF-α)(4).

Page 21, lines 19-30:

Seminal vesicle fluid was fractionated by size exclusion chromatography in order to identify GM-CSF-stimulating activity. Two fractions were identified; a high molecular weight (650 kDA) proteinacous moiety and a intermediate molecular weight, more heterogenous moiety eluting between 150-440 kDA (10.62). The latter moiety was identified as TGFβ$_1$, on the basis of findings that ~~it's~~ its GM-CSF stimulating activity was enhanced by acid activation, that TGFβ$_1$, immunoactivity and bioactivity co-eluted in the same fraction, and that anti-TGFβ$_1$ ~~neutralising~~ neutralizing antibody could block the GM-CSF stimulating activity of this fraction (Figures 1,2). The molecular weight of GM-CSF stimulating activity in seminal vesicle fluid (150-440 kDa) is consistent with that of the latent form of TGFβ$_1$, a complex of 230-290 kDa which comprises ~~of~~ the mature TGF-β dimer (25 kDa) non-covalently associated with a 75-80 kDa latency associated protein and a 130-190 kDa binding protein (23).

Page 23, lines 20-26:

To test the importance of exposure to seminal ~~reside~~ vesicle fluid for pregnancy success, Balb/c F1 females were mated with CBA males from which the seminal vesicles had been surgically removed (SV-studs). No implantation sites were present in the uterus on day 17 of pregnancy (n=12 females). This total infertility was not due to a

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lack of ~~fertilisation~~ fertilization, but rather was associated with implantation failure or early fetal resorption. This may reflect insufficient maternal tolerance of the semi-allogeneic embryos due to the lack or exposure to seminal ~~reside~~ vesicle fluid TGFβ at mating.

Page 27, line 30 through Page 28, line 4:

Induction of Th 1 hypo-responsiveness against paternal antigens has been reported to result in an improved pregnancy outcome in women previously experiencing recurrent miscarriage ~~(102)~~. While no data exist on the ability of paternal antigen/TGFβ immunisation to initiate Th 1 hypo-responsiveness against paternal antigens, or to deviate previously existing Th 1 immune responses in women, nor on the ability of TGFβ to improve reproductive outcome, this is likely to be the case. The inventors have been the first to conduct a large ~~randomised~~ randomized, controlled trial investigating the effect of semen exposure on IVF treatment outcome. This trial has confirmed that women exposed to semen (containing paternal antigen and natural TGFβ) around the time of thawed embryo transfer have a reduced risk of early embryonic loss compared to those instructed to abstain (Table VI). This improvement in reproductive outcome is likely to be mediated by maternal immune tolerance towards paternal antigens initiated by TGFβ and seminal antigens at the time of intercourse.

Page 29, lines 18-22:

Pregnancy outcome following thawed embryo transfer. Patient characteristics were not significantly different between the two groups. ~~An~~ A biochemical pregnancy was

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defined as one serum βHCG exceeding 25 IU and a clinical pregnancy as a conceptus/fetal pole seen at ultrasound at 6 weeks gestation. Statistical analysis was performed using the Chi square calculation. NS=not significant. *=one twin pregnancy.

Page 29, lines 33-34:

6. ~~Clarke~~ Clark (1984) in Immunological aspects of reproduction in mammals, ed. Crighton, (Butterworths, London), pp. 153-182.

Page 31, line 26:

70. ~~Medwar~~ Medawar PB (1953) *Symp Soc Exp Biol* **44**, 320-38.

marked paragraphs

ATTACHMENT C

Marked Up Replacement Claims

Following herewith is a marked up copy of each rewritten claim.

50. (Twice Amended) A method of ~~eliciting an immune reaction in a prospective mammalian mother to one or more antigens of a prospective father to alleviate~~ alleviating symptoms of an infertility condition in a mammalian prospective mother, said method comprising:

exposing ~~said~~ the prospective mother to ~~said~~:

a) one or more MHC Class I antigens of ~~said~~ a prospective father, and

b) ~~to~~ a substantially purified TGFβ selected from the group consisting of $TGF\beta_1$, $TGF\beta_2$, $TGF\beta_3$ and activin,

~~said method leading~~ thereby to induce tolerance to said ~~one or more~~antigen or antigens ~~and alleviation of symptoms of said infertility condition~~.

56. (Twice Amended) The method according to claim 51, wherein ~~said~~ the TGFβ and ~~said~~ the MHC Class I antigen ~~one~~ or ~~more~~ antigens are each administered at a first site and a different site respectively.

57. (Twice Amended) The method according to claim 50, wherein ~~said~~the TGFβ and ~~said~~ the MHC Class I antigen ~~one~~ or ~~more antigen~~antigens are administered temporarily spaced apart.

64. (Twice Amended) The method according to claim 50, wherein the MHC Class I antigen ~~one~~ or ~~more~~ antigens ~~are~~ administered ~~on~~ are from sperm cells of the prospective father.

65. (Twice Amended) The method according to claim 51, wherein the MHC Class I antigen ~~one~~ or ~~more~~ antigens ~~are~~ administered ~~on~~ are from sperm cells of the prospective father.

marked claims